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- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): BATES, Susan, E. [US/US]; 5402 Alta Vista Road, Bethesda, MD 20814 (US). FOJO, Antonio, T. [US/US]; 118 New Mark Esplanade, Rockville, MD 20814 (US). PIEKARZ, Richard [US/US]; 8708 First Avenue No. 309, Silver Spring, MD 20910 (US).
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(54) Title: METHODS OF TREATING CUTANEOUS T-CELL LYMPHOMA AND PERIPHERAL T-CELL LYMPHOMA (UNSPECIFIED) BY ADMINISTERING A HISTONE DEACETYLASE INHIBITOR

(57) Abstract: The present invention provides methods of treating cutaneous T-cell lymphoma and peripheral T-cell lymphoma, unspecified, in a mammal. The methods comprise administering to the mammal an effective amount of a histone deacetylase inhibitor.

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METHODS OF TREATING CUTANEOUS T-CELL LYMPHOMA AND
PERIPHERAL T-CELL LYMPHOMA (UNSPECIFIED) BY
ADMINISTERING A HISTONE DEACETYLASE INHIBITOR

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to methods of treating cutaneous T-cell lymphoma and peripheral T-cell lymphoma (unspecified). The methods comprise administering a histone deacetylase inhibitor.

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BACKGROUND OF THE INVENTION

Cutaneous T-cell lymphoma is an indolent disorder of malignant, relatively mature T-cells which frequently involves the skin, bloodstream, regional lymph nodes and spleen. Approximately 800-1,000 new cases are diagnosed per year in the U.S.

15 There are several clinical variants of the disease. The condition causes severe skin itching, pain and edema. Currently, cutaneous T-cell lymphoma is treated topically with steroids, photochemotherapy and chemotherapy. Radiotherapy is also utilized.

Peripheral T-cell lymphomas (WHO classification) originate from mature or peripheral (not central or thymic) T-cell lymphocytes as a clonal proliferation from a single T-cell and are usually either predominantly nodal or extranodal tumors. They have T-cell lymphocyte cell-surface markers and clonal rearrangements of the T-cell receptor genes.

20 The present invention seeks to provide new methods of treating cutaneous T-cell lymphoma and peripheral T-cell lymphoma, unspecified. The present inventive method of treating cutaneous T-cell lymphoma offers advantages over currently available methods by effectively treating the severe skin itching, pain and edema that accompany the disease without causing side effects. These objects and these advantages, as well as additional objects, advantages and inventive features, will become apparent upon reading the detailed description provided herein.

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BRIEF DESCRIPTION OF THE INVENTION

The present invention provides methods of treating cutaneous T-cell lymphoma and peripheral T-cell lymphoma, unspecified, in a mammal. The methods comprise administering to the mammal an effective amount of a histone deacetylase

inhibitor. Preferably, the histone deacetylase inhibitor is a depsipeptide, in particular the depsipeptide known as NSC 630176. The methods can further comprise (i) administering a steroid, a P-glycoprotein multiple drug resistance (MDR) antagonist, an active agent targeted to a T-cell receptor and/or a retinoid, (ii) the use of
5 chemotherapy, and/or (iii) the use of photochemotherapy.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated on the surprising and unexpected discovery that NSC 630176, a depsipeptide that inhibits histone deacetylase,
10 effectively treats cutaneous T-cell lymphoma and peripheral T-cell lymphoma, unspecified. Thus, the present invention provides methods of treating cutaneous T-cell lymphoma and peripheral T-cell lymphoma in a mammal. The methods comprise administering to the mammal an effective amount of a histone deacetylase inhibitor.

Histone deacetylase inhibitors are known in the art. Examples of histone
15 deacetylase inhibitors include, but are not limited to, trapoxin A, trapoxin B, trichostatin A, amide analogues of trichostatin A (see, e.g., Jung et al., *J. Med. Chem.* 42: 4669-4679 (1999)), trichostatin C, sodium butyrate (including derivatives thereof, such as phenyl butyrate), phenyl acetate, 3-bromopropionate, HC toxin, apicidin, and depsipeptides, such as (E)-(1S, 4S, 10S, 21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-
20 oxa-12,13-dithia-5,8,20,23-tetraazabicyclo [8,7,6]-tricos-16-ene-3,6,19,22-pentanone (NSC 630176, which is also known as FR901228), and the cyclic depsipeptides didemnin B and sandramycin. Preferably, the histone deacetylase inhibitor is a depsipeptide. More preferably, the depsipeptide is NSC 630176.

Preferably, the histone deacetylase inhibitor is administered in the form of a
25 pharmaceutically acceptable composition (see, e.g., Remington's Pharmaceutical Sciences, 17th ed., (Mack Publishing Company, Philadelphia, Pa.: 1985), and Langer, Science, 249, 1527-1533 (1990)) suitable for topical administration. Such compositions are known in the art. A formulation suitable for topical application can be in the form of creams, ointments, or lotions in which the inhibitor can be mixed
30 with conventional oleaginous or emulsifying excipients.

Alternatively and also preferably, the histone deacetylase inhibitor is systemically administered. If the histone deacetylase inhibitor is systemically administered, preferably it is administered orally or by intravenous infusion. Compositions suitable for oral and intravenous infusion are also known in the art.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluent, such as water, saline, or orange juice; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as solids or granules; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth. Pastilles can comprise the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients/carriers as are known in the art.

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described. When the histone deacetylase inhibitor is administered systemically, preferably the administration is intermittent. For example, if the histone deacetylase inhibitor NSC 630176 is administered by intravenous infusion, it can be administered at the maximum tolerated dose of 17.8 mg/m² over 4 hours on days 1 and 5 of a 21-day cycle, for example, although other doses and schedules can be effective and can be determined in accordance with methods known in the art.

By "effective amount" is meant an amount of histone deacetylase inhibitor sufficient to treat the cutaneous T-cell lymphoma or peripheral T-cell lymphoma, unspecified, in the mammal, in particular a human, over a reasonable time frame. The determination of an effective amount is within the ordinary skill in the art. The dose administered to a mammal, particularly a human, in the context of the present invention

will vary with the inhibitor administered (e.g., its potency), the composition employed, the route of administration, the severity of the disease state, the body weight and age of the infected individual, the extent of contact, and the particular site being treated. The size of the dose also will be determined by the existence of any adverse side effects
5 that can accompany the use of the particular inhibitor employed. It is always desirable, whenever possible, to keep adverse side effects to a minimum.

Generally, when an above-described inhibitor is administered to an animal, such as a mammal, in particular a human, it is preferable that the inhibitor is administered in a dose of from about 1 to about 1,000 micrograms of the inhibitor per kg of the body
10 weight of the host per day when given parenterally. However, this dosage range is merely preferred, and higher or lower doses may be chosen in appropriate circumstances. For instance, the actual dose and schedule can vary depending on whether the composition is administered in combination with other pharmaceutical compositions, or depending on interindividual differences in pharmacokinetics, drug
15 disposition, and metabolism. One skilled in the art easily can make any necessary adjustments in accordance with the necessities of the particular situation. The maximum tolerated dose of NSC 630176 is 17.8 mg/m².

The methods can further comprise (i) administering a steroid, a P-glycoprotein multiple drug resistance (MDR) antagonist, a retinoid and/or an active agent targeted
20 to a T-cell receptor, (ii) the use of chemotherapy, and/or (iii) the use of photochemotherapy.

Examples of steroids that are suitable for use in the context of the present invention are known in the art and include, but are not limited to, glucocorticoids. Preferably, a steroid is administered topically.

25 P-glycoprotein antagonists are also known in the art and include, but are not limited to, cyclosporin A, verapamil, quinidine, dihydro-pyridines, calcium channel blockers, cyclosporin analogues (e.g., PSC833 (Novartis, East Hanover, NJ)), phenothiazines, thioxanthenes, XR9576 (Xenova, Flough, United Kingdom), GG918 (glaxo), VX710 (Vertex), and others of similar or greater potency. Preferably, a P-
30 glycoprotein antagonist is administered topically or systemically.

Retinoids include agents that bind to the retinoic acid receptor, such as 9-*cis*-retinoic acid, 4-hydroxy-retinoic acid, all *trans*-retinoic acid, (E)-4-[2-(5,6,7,8-tetrahydro-2-naphthylenyl)-1-propenyl]-benzoic acid, 3-methyl-(E)-4-[2-(5,6,7,8-

tetrahydro-2-naphthylenyl)-1-propenyl]-benzoic acid), and the like as known in the art. A retinoid is preferably administered topically or systemically.

An active agent that is targeted to a T-cell receptor can be any suitable agent that is targeted to a T-cell receptor, such as the IL-2 receptor, and has an effect, which, desirably, is an anti-cancer effect. The active agent can be an antibody (or an antigenically reactive fragment thereof) to a T-cell receptor, such as the IL-2 receptor. A commercially available antibody to a T-cell receptor is Zenapax, which is available from Hoffman-LaRoche, Inc., Nutley, NJ. The antibody is preferably administered systemically. Alternatively, the active agent can be a fusion protein or a conjugate of a means of targeting a T-cell receptor, such as an antibody (or an antigenically reactive fragment thereof) to a T-cell receptor or a ligand to a T-cell receptor, and an active agent, such as a drug (or a prodrug or derivative or pharmaceutically acceptable salt thereof) or a toxin as are known in the art. Desirably, the drug is an anti-cancer drug and the toxin is an anti-cancer toxin. An example of such an agent is an anti-IL-2 antibody fused to a toxin, such as the agent known as OntakTM (Ligand Pharmaceuticals, San Diego, CA).

EXAMPLES

The following examples serve to illustrate the present invention and are not intended to limit its scope in any way.

Example 1

This example describes the treatment of cutaneous T-cell lymphoma in four adult human males.

Patient A

At the time that treatment was initiated, the male had skin (nodules on elbows, buttocks, sole of right foot (4 cm in size) and legs), lymph node and bone marrow involvement, retroperitoneal adenopathy, sinusitis, and mild erythroderma. He had previously received one course of EPOCH chemotherapy and the disease progressed after the course of treatment. He then was treated with five cycles of an infusion of depsipeptide (17.8 mg/m² on days 1 and 5 of a 21 day cycle). No change was noticed after the first cycle. The sinusitis improved after the second cycle as did the erythroderma and the skin nodules. Over the course of the five cycles of treatment,

the patient experienced a steady decrease in the size of the subcutaneous nodules until most of them were no longer palpable. The nodule on the sole of the right foot decreased from 4 cm to 0.5 cm. The erythroderma improved and the sinusitis disappeared.

5

Patient B

The patient began treatment after a 4-5 year history of pruritic skin lesions that started behind the ears and gradually spread to encompass his entire body. Skin biopsies indicated mycosis fungoides. Disease progressed following three cycles of CVP (cyclophosphamide, vincristine and prednisone). At the time of initiation of treatment (as indicated for patient A), his peripheral white blood cell count was greater than 40,000 and comprised mostly Sezary cells. Following the first cycle of treatment, a decline in white blood cells was noted. Following the second and third cycles of treatment, a decrease in skin edema and thickening and a continued improvement in Sezary cell count were observed with marked relief of symptoms.

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Patient C

The patient had been treated with CHOP for approximately 3 1/2 months and with Yttrium-labeled Zenapax for approximately six weeks. He had severe erythroderma and lymphadenopathy. After the first cycle of treatment (as indicated for patient A), there was a marked decrease in skin edema, redness and itching. After three cycles of treatment, a decrease in skin edema and thickening and a continued improvement in Sezary cell count (decreased from 80,000 to 6,000) were observed with marked relief of symptoms.

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Patient D

The patient presented with tumor-stage cutaneous T-cell lymphoma. He was symptomatic with mild generalized pruritus. His entire skin was covered with hundreds of tumors. The lesions had developed within the previous four months and were not amenable to treatment with total skin electron beam therapy or other topical therapies.

30

Treatment of the patient with depsipeptide was begun (as indicated for patient A). After administering the second dose of depsipeptide of the first cycle of treatment, fine needle aspirations of two lesions were performed. A cytological

examination showed many cells with cytoplasmic vacuolization and nuclear fragmentation, suggesting that a significant population of the tumor cells was affected by the treatment.

After six cycles of treatment, almost all of the tumors cleared. Five lesions
5 that had initially responded to treatment eventually progressed through therapy and were treated with radiation.

Example 2

This example describes the treatment of peripheral T-cell lymphoma,
10 unspecified, in an adult human male.

Physical examination of this patient revealed the presence of erythematous
plaques of the skin with nodules over the elbows, buttocks and thighs. A large 3-4 cm
mass was present over the plantar surface of the left foot. The bone marrow was not
involved. A CT scan of the chest, abdomen and pelvis showed mediastinal,
15 retrocrural, axillary, retroperitoneal, pelvic and inguinal adenopathy.

After one cycle of EPOCH chemotherapy, the patient experienced progression
of his subcutaneous nodules and erythema and was enrolled on the phase I
depsipeptide study. After initiation of depsipeptide treatment (as indicated for patient
A in Example 1), there was clearing of his cutaneous lesions, skin nodules and
20 lymphadenopathy on CAT scan. He was declared to be in complete remission after
the eighth cycle of depsipeptide treatment.

All of the references cited herein, including patents, patent applications, and
publications, are hereby incorporated in their entireties by reference.

25 While this invention has been described with an emphasis upon preferred
embodiments, it will be obvious to those of ordinary skill in the art that variations of the
preferred embodiments may be used and that it is intended that the invention may be
practiced otherwise than as specifically described herein. Accordingly, this invention
includes all modifications encompassed within the spirit and scope of the invention as
30 defined by the following claims.

WHAT IS CLAIMED IS:

1. A method of treating cutaneous T-cell lymphoma in a mammal, which method comprises administering to the mammal an effective amount of a histone deacetylase inhibitor, whereupon the cutaneous T-cell lymphoma in the mammal is
5 treated.
2. The method of claim 1, wherein the histone deacetylase inhibitor is a depsipeptide.
- 10 3. The method of claim 2, wherein the depsipeptide is (E)-(1S, 4S, 10S, 21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8,7,6]-tricos-16-ene-3,6,19,22-pentanone (NSC 630176).
4. The method of claim 1, wherein said administering is topically or
15 systemically.
5. The method of claim 4, wherein systemically administering is administering orally or by intravenous infusion.
- 20 6. The method of claim 5, wherein systemically administering is intermittently.
7. The method of claim 6, wherein said histone deacetylase inhibitor is NSC 630176 and 17.8 mg/m² of NSC 630176 are administered by intravenous infusion on
25 days 1 and 5 of a 21-day cycle.
8. The method of claim 1, which further comprises one or more of the following:
 - (i) administering a steroid, a P-glycoprotein multiple drug resistance
30 (MDR) antagonist, a retinoid, and/or an active agent targeted to a T-cell receptor,
 - (ii) the use of chemotherapy, and
 - (iii) the use of photochemotherapy.

9. The method of claim 8, wherein the histone deacetylase inhibitor is a depsipeptide.

10. The method of claim 9, wherein the depsipeptide is NSC 630176.

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11. The method of claim 8, wherein said administering is topically or systemically.

12. The method of claim 11, wherein systemically administering is
10 administering orally or by intravenous infusion.

13. The method of claim 12, wherein systemically administering is intermittently.

14. The method of claim 13, wherein the histone deacetylase inhibitor is NSC
15 630176 and 17.8 mg/m² of NSC 630176 are administered by intravenous infusion on days 1 and 5 of a 21-day cycle.

15. A method of treating peripheral T-cell lymphoma, unspecified, in a
20 mammal, which method comprises administering to the mammal an effective amount of a histone deacetylase inhibitor, whereupon the peripheral T-cell lymphoma, unspecified, in the mammal is treated.

16. The method of claim 15, wherein the histone deacetylase inhibitor is a
25 depsipeptide.

17. The method of claim 16, wherein the depsipeptide is (E)-(1S, 4S, 10S,
21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-
tetraazabicyclo [8,7,6]-tricos-16-ene-3,6,19,22-pentanone (NSC 630176).

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18. The method of claim 15, wherein said administering is topically or systemically.

19. The method of claim 18, wherein systemically administering is administering orally or by intravenous infusion.

20. The method of claim 19, wherein systemically administering is
5 intermittently.

21. The method of claim 20, wherein said histone deacetylase inhibitor is NSC 630176 and 17.8 mg/m² of NSC 630176 are administered by intravenous infusion on days 1 and 5 of a 21-day cycle.

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22. The method of claim 15, which further comprises one or more of the following:

- (i) administering a steroid, a P-glycoprotein multiple drug resistance (MDR) antagonist, a retinoid, and/or an active agent targeted to a T-cell
15 receptor,
(ii) the use of chemotherapy, and
(iii) the use of photochemotherapy.

23. The method of claim 22, wherein the histone deacetylase inhibitor is a
20 depsipeptide.

24. The method of claim 23, wherein the depsipeptide is NSC 630176.

25. The method of claim 22, wherein said administering is topically or
25 systemically.

26. The method of claim 25, wherein systemically administering is administering orally or by intravenous infusion.

27. The method of claim 26, wherein systemically administering is
30 intermittently.

28. The method of claim 27, wherein the histone deacetylase inhibitor is NSC 630176 and 17.8 mg/m² of NSC 630176 are administered by intravenous infusion on days 1 and 5 of a 21-day cycle.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/15 A61K45/06 A61P35/00

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 39965 A (BEACON LAB L L C) 17 September 1998 (1998-09-17)</p> <p>page 1, line 16 - line 35; claims 1,6,9,41 page 2, line 1 - line 6 page 3, line 6 - line 12 page 5, line 22 -page 8, line 5 page 9, line 29 -page 10, line 1 page 19, line 16 - line 35</p> <p style="text-align: center;">-/--</p>	<p>1,4-6,8, 11-13, 15, 18-20, 22,25-27</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHESON, BRUCE D. ET AL: "New drugs for the treatment of chronic lymphocytic leukemia" REVIEWS IN CLINICAL AND EXPERIMENTAL HEMATOLOGY (2000), 4(2), 145-166 , XP002226646 page 154, left-hand column, paragraph 1 - paragraph 3 -----	1-7, 15-21
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A	MERTINS, S. D. (1) ET AL: "Development of depsipeptide FR901228, a histone deacetylase inhibitor, as an anticancer agent." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, (MARCH, 1999) VOL. 40, PP. 623. MEETING INFO.: 90TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH PHILADELPHIA, PENNSYLVANIA, USA APRIL 10-14, 1999 AMERICAN , XP008010161 the whole document -----	1,15
A	JUNG M ET AL: "Amide analogues of trichostatin A as inhibitors of histone deacetylase and inducers of terminal cell differentiation." JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES 4 NOV 1999, vol. 42, no. 22, 4 November 1999 (1999-11-04), pages 4669-4679, XP002226647 ISSN: 0022-2623 cited in the application page 4669, left-hand column, paragraph 2 page 4674, left-hand column, paragraph 2 -----	1,15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/25827

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1, 4, 8, 11-13, 15, 18-20, 22, 25-27
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,4,8,11-13,15,18-20,22,25-27

Present claims 1,4,8,11-13,15,18-20,22,25-27 relate to a compound defined by reference to a desirable characteristic or property, namely the use of a histone deacetylase inhibitor for the treatment of cutaneous T-cell lymphoma.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the inhibitors as described in Claims e.g. 2, 3 and 7, and those mentioned in the description at the page 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/25827

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9839965	A	17-09-1998	US 6124495 A	26-09-2000
			AU 746268 B2	18-04-2002
			AU 6549698 A	29-09-1998
			EP 0973388 A1	26-01-2000
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